REMARKS

Reconsideration of the application is respectfully request in view of the foregoing amendment and the following remarks.

Claims 23-26 are pending in the application. Claims 23-26 have been rejected. Claim 23 has been amended and claims 24 and 26 have been cancelled without prejudice. As claims 24 and 26 have been cancelled the rejections are applicable to claims 23 and 25.

Claims 23-26 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,313,139 and claims 7 and 8 of U.S. Patent No. 6,080,773.

In response to this rejection, two terminal disclaimers are submitted herewith, disclaiming the term of any patent that would extend beyond the expiry of U.S. Patent Nos. 6,313,139 and 6,080,773.

In view of the above, withdrawal of the rejection of claims 23 and 25 under the ground of nonstatutory obviousness-type double patenting is respectfully requested.

Claims 23-26 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner states:

> ...the specification, while being enabling for the compounds disclosed by the instant specification for treating a psychiatric disorder by administering an Ih channel inhibitor having a pIC50 of 5 to 12 for inhibition of the hyperpolarization-activated cation current in dorsal root ganglion cells, does not reasonably provide enablement for any compound presently known or will become known in the future which is an Ih channel inhibitor having a pIC50 of 5 to 12 for inhibition of the hyperpolarization-activated cation current in dorsal root ganglion cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims...one skilled in the art could not use the claimed invention without undue experimentation.

The Examiner further discusses the Wands factors in her assessment of lack of enablement. An analysis of the Wands factors with reference to the Examiner's comments is provided below.

Nature of the Invention

The Examiner essentially contends that 1) the present claims do not recite a particular genus of compounds to represent an Ih channel inhibitor, and 2) Applicants are asserting that any compound, because of its mode of action, which involves being an Ih channel modulator (see page 11 of Office Action), would be useful for treating all psychiatric disorders.

In response, the present invention as set forth in amended independent claim 23 involves a method of treating anxiety. In contrast to the Examiner's assertion that this method utilizes an Ih channel modulator, this method utilizes an Ih channel inhibitor which has a pIC50 value of 5 to 12.

Amount of Direction or Guidance Presented and the Presence or Absence of Working Examples

The Examiner contends 1) that a single class of compound can be used to treat all psychiatric disorders is an incredible finding for which Applicants have not provided evidence, and 2) that Applicants have not provided competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating all psychiatric disorders by administering any compound that can be classified as an Ih channel inhibitor.

As stated above, amended claim 23 is directed to a method for treating anxiety, and not any and all psychiatric disorders, utilizing an Ih channel inhibitor. The compounds identified as Ih channel inhibitors have high selectivity when tested for their *in vitro* activity against a wide range of other receptor and Ion channel targets. In view of this finding the skilled person would expect that the observed anti-anxiety activity of these compounds would be attributable to their Ih channel blocking properties and conversely compounds which have Ih channel blocking properties would be expected also to have anti-anxiety activity.

The present application also provides experimental data which demonstrates that there is a correlation between inhibition of the Ih channels and anti-anxiety activity as evidenced by the results in mice utilizing the marble burying test (see Tables 1 and 2; pages 24 and 25). Accordingly, the skilled person armed with this evidence would readily expect that all Ih channel inhibitors having a pIC50 value of 5 to 12 would possess anti-anxiety activity and therefore be useful in a method for treating anxiety. For this conclusion, it is therefore not necessary to first know the structure of the Ih inhibitor in question.

Breadth of the Claims

The Examiner indicates that the breadth of the claims is treating all psychiatric disorders by administering any Ih channel inhibitor which has a pIC50 of 5 to 12.

As discussed above, amended claim 23 is directed to a method for treating anxiety utilizing an Ih channel inhibitor which has a particular pIC50 range of 5 to 12. The present application provides evidence demonstrating that the described compounds inhibit Ih channels and that there is a correlation between inhibition of these channels and anti-anxiety acitivty as evidenced in mice by the marble burying test. As one skilled in the art armed with this evidence would readily conclude that other compounds that inhibit Ih channels would also possess such anti-anxiety activity, it is believed that the present specification is commensurate in scope with amended claim 23.

The Quantity of experimentation Needed

The Examiner essentially contends the nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activity for each disorder presently claimed and that the quantity of experimentation would be undue to test for all psychiatric disorders.

In response, Applicants have provided experimental evidence demonstrating that compounds that function as Ih channel inhibitors possess an anti-anxiety activity. In addition, as the present specification describes 1) how to determine the potency of a compound to inhibit Ih channels and the pIC50 value for inhibition of Ih channels, and 2) a specific test in mice for determining the compound's effect on anxiety, one skilled in the art would be provided with sufficient guidance to test whether other compounds also block the Ih channel. Thus, the amount of experimentation would not be undue, but instead would constitute routine experimentation.

The Level of Skill in the Art

The Examiner contends that even though the level of skill in the art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance, one skilled in the art could not use the claimed invention without undue experimentation.

Applicants agree that the level of skill in the art is very high. One of such high skill armed with objective evidence in the specification correlating inhibition of Ih channels to anti-anxiety activity, and methods of how to determine Ih activity and the pIC50 value for Ih channel inhibition, would be readily able to determine other compounds that are Ih channel inhibitors and utilize the claimed invention without undue experimentation.

With respect to the Examiner's assertion pertaining to the unpredictable nature of the invention and state of the art, it is duly noted that a specification is presumed to be in compliance with the enablement requirement, unless there is reason to doubt the objective truth of the statements contained therein. As stated by the Federal Circuit, in *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (CCPA 1971)

> "it is incumbent upon the Patent Office, whenever a rejection on this basis [112, first paragraph] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence [emphasis added] or reasoning which is inconsistent with the contested statement."

In the present case as stated above, Applicants have provided objective evidence demonstrating that compounds that inhibit Ih channels possess anti-anxiety activity. The Examiner, in merely providing the afore-mentioned blanket assertion that the invention and state of the art are unpredictable, has failed to provide any objective evidence, i.e., prior art references, etc., which cast doubt that any compound that possesses such Ih channel inhibitory

activity would also possess an anti-anxiety effect. Accordingly, the Examiner has not met her initial burden of providing objective evidence to back up her assertion of lack of enablement as is required by law.

In sum, the totality of Wands factors, when considered as a whole, does reasonably enable the claimed method for treating anxiety.

In view of the above, withdrawal of the rejection of claims 23 and 25 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 23-26 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner contends that the metes and bounds of these claims cannot be ascertained since a compound that meets the definition of an Ih channel inhibitor is not recited in the instant claims. Applicants respectfully traverse this rejection and submit that that the term "Ih channel inhibitor" is definite.

As discussed above, Applicants have provided compounds that inhibit Ih channels, and have provided ample guidance by way of the present specification on 1) how to determine whether a compound inhibits an Ih channel, 2) how to determine pIC50 values, and 3) how to test such compounds *in vivo* by way of animal models (mice marble burying test) to ascertain their effect on anxiety. Thus, one skilled in the art armed with this disclosure would readily be able to distinguish compounds that are Ih channel inhibitors possessing the requisite pIC50 value from those compounds that are not Ih channel inhibitors possessing the requisite pIC50 value. Accordingly, the metes and bounds of the term "Ih channel inhibitor" would be readily understood by one of high skill in the art.

In view of the above, withdrawal of the rejection of claims 23 and 25 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 23-26 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,894,376 (Morad et al.). In particular, the Examiner contends that Morad et al. disclose the compounds in column 4, lines 57-63, which are useful for treating psychiatric disorders such as manic depressive illness. Applicants respectfully traverse this rejection and submit that Morad et al. does not anticipate amended claim 23.

Morad et al. is directed to certain guanidine derivatives which are shown to selectively suppress T type calcium channels. No where does Morad et al. describe that these guanidine derivatives are Ih channel inhibitors. In addition, the compounds described in Morad et al. have a guanidine functional group which is absent from the compounds described in the present invention as being Ih channel inhibitors. Since Morad et al. does not describe that its compounds inhibit Ih channels and does not identically describe the same compounds as are set forth in the present specification, Morad et al. does not anticipate amended claim 23.

In view of the above, withdrawal of the rejection of claims 23 and 25 under 35 U.S.C. §102(b) is respectfully requested.

Claims 23-26 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Morad et al. The Examiner contends that Morad et al. teach that psychiatric disorders can be treated by administering a substituted pyrazinoylguanidine such as amiloride. The Examiner further contends that one skilled in the art would be motivated to administer products embraced by the prior art to arrive at the present invention with the expectation of treating psychiatric disorders. Applicants respectfully traverse this rejection and submit that claims 23 and 25 are not made obvious by Morad et al.

As stated above, Morad et al. relate to particular guanidine derivatives which are described as suppressing T type calcium channels. Morad et al. does not teach or specifically suggest that its compounds are Ih channel inhibitors. In addition, the compounds of Morad et al. have a guanidine functional group which is absent from the compounds described in the present specification as being Ih channel inhibitors. As Morad et al. doe not teach or specifically suggest that its compounds are Ih channel inhibitors, there is no implication to the skilled person that the compounds of Morad et al. would be relevant as Ih channel inhibitors or that such Ih channel inhibitors would be useful to treat anxiety. Accordingly, one skilled in the art reading Morad et al. would not be motivated to contemplate a method of treating anxiety using Ih channel inhibitors.

In view of the above, withdrawal of the rejection of claims 23 and 25 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below.

Respectfully submitted,

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